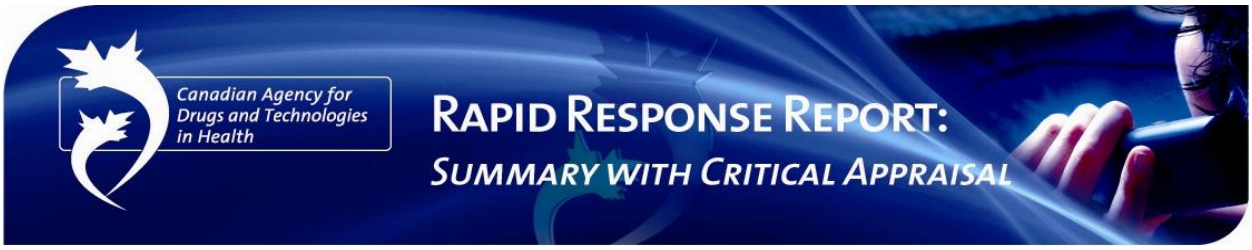

TITLE: NS5B and NS3 Inhibitors in Patients with Resistance-Associated Variants of Hepatitis C Virus: A Review of the Clinical Effectiveness

DATE: 08 August 2016

CONTEXT AND POLICY ISSUES

Hepatitis C virus (HCV) infection is a serious health problem worldwide.[1] It is estimated that approximately 150 to 170 million individuals worldwide are infected with HCV and that greater than 350,000 deaths occur annually due to HCV related complications.[2,3] Chronic HCV infection is the leading cause of cirrhosis, hepatocellular carcinoma, and end-stage liver disease requiring liver transplantation.[3,4] It is estimated that 50% to 75% of individuals currently infected with HCV are undiagnosed and are untreated, and many of them will have progression to cirrhosis, hepatocellular carcinoma or other liver complications. At the end of 2011, it was estimated that 220,697 to 245,987 Canadians were living with chronic HCV infection which is equivalent to 0.6% to 0.7% of the total Canadian population.[5] HCV has six major genotypes (GTs) and genotype 1 (GT 1) is most prevalent in North America.[6,7] In Canada, among those infected with HCV, 65% have GT 1 (56% GT 1a and 33% GT 1b, and 10% with unspecified subtype or mixed infection), 14% have GT 2, 20% have GT 3 and GT 4, 5, and 6 are rare (<1% of HCV cases).[7,8]

HCV is a single-stranded RNA virus that encodes for a polyprotein leading to the formation of four structural and six nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B).[2] HCV infection is associated with morbidity and mortality and the aim of treatment is to achieve a sustained virological response (SVR).[6] SVR has been defined as negative or undetectable HCV RNA test results at generally 12 or 24 weeks post treatment.[9,10] Treatment for HCV infection includes interferon and ribavirin (R) based therapy, and more recently, therapy with direct acting antivirals (DAAs) have been introduced. DAAs directly inhibit essential HCV proteins required for viral replication.[11] DAAs include NS3/4A inhibitors, NS5A inhibitors and NS5B inhibitors which respectively target three HCV proteins: NS3/4A protease, and NS5A and NS5B RNA-dependent polymerase.[12] NS5B inhibitors approved in Canada include sofosbuvir (SOF) and dasabuvir (DSV). NS3 inhibitors approved in Canada include simeprevir (SMV), grazoprevir (GZR), asunaprevir (ASV), paritaprevir (PRV), boceprevir (BOC), and telaprevir (TVR). Recently, the use of BOC and TVR has been discontinued in Canada.[13,14] There is a suggestion that resistance associated variants (RAVs) of these proteins may impact SVR rates achieved by

therapy.[15] There is some debate as to whether testing and identification of HCV RAVs by sequencing, either before treatment (baseline) or after failure, would be useful to guide optimal therapy selection.

The purpose of this report is to review the comparative clinical effectiveness of HCV pharmacotherapies containing NS3 or NS5B inhibitors in DAA–naive and DAA-experienced patients infected with HCV and with or without NS3 or NS5A RAVs at baseline (i.e. at initiation of treatment for DAA-naïve patients or at initiation of retreatment for patients who had failed prior DAA containing treatment regimens).

RESEARCH QUESTIONS

1. What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS5B inhibitors in direct-acting antiviral–naive patients infected with NS5B resistance-associated variants of hepatitis C virus at baseline?

2. What is the clinical effectiveness of hepatitis C pharmacotherapies in direct-acting antiviral–experienced patients infected with treatment-emergent NS5B resistance-associated variants of hepatitis C virus?

3. What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS3 protease inhibitors in direct-acting antiviral–naive patients infected with NS3 protease inhibitor resistance-associated variants of hepatitis C virus at baseline?

4. What is the clinical effectiveness of hepatitis C pharmacotherapies in direct-acting antiviral–experienced patients infected with treatment-emergent NS3 protease inhibitor resistance-associated variants of hepatitis C virus?

KEY FINDINGS

Evidence suggests that in direct acting antiviral (DAA) treatment-naïve patients who were infected with hepatitis C virus (HCV), genotype (GT) 1, the sustained virological response (SVR) rates with sofobusvir (SOF) or with paritaprevir (PRV) ± dasabuvir (DSV) containing treatment regimens were comparable between patients with and without NS5B resistance associated variants (RAVs).

Evidence suggests that in DAA treatment experienced patients who were infected with HCV GT1, the SVR rates with SOF containing treatment regimens were comparable between patients with and without NS5B RAVs.

Evidence suggests that in DAA treatment-naïve patients who were infected with HCV GT1, the SVR rates with asunaprevir or grazoprevir containing treatment regimens were comparable between patients with and without NS3 RAVs; and the SVR rates with PRV or simeprevir containing regimens varied depending on the other drugs that were used in combination in these regimens.

Evidence suggests that in DAA treatment experienced patients who were infected with HCV GT1 the majority of patients with NS3 RAVs achieved SVR with retreatment with GRZ containing regimens; the SVR rates for retreatment with simeprevir containing regimens varied

depending on whether it was used in combination with daclatasvir or pegylated interferon and ribavirin.

Some studies included only few patients and the numbers of patients with NS5B or NS3 RAVs were small compared with the numbers of patients without the RAVs, hence the finding need to be interpreted in the light of these limitations.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and July 8, 2016

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients infected with HCV genotypes 1 to 6, including subtypes 1a and 1b
Intervention	Q1: Hepatitis C pharmacotherapies containing NS5B polymerase inhibitors (e.g., sofosbuvir, dasabuvir) in direct-acting antiviral–naive patients with baseline NS5B resistance-associated variants of HCV Q2: Longer treatment duration with hepatitis C pharmacotherapies (with or without ribavirin), adding drugs, or switching treatment regimens in direct-acting antiviral–experienced patients with treatment-emergent NS5B resistance-associated variants of HCV Q3: Hepatitis C pharmacotherapies containing NS3 protease inhibitors (simeprevir, grazoprevir, asunaprevir, paritaprevir) in direct-acting antiviral–naive patients with baseline NS3 protease inhibitor resistance-associated variants of HCV (e.g., Q80K) Q4: Longer treatment duration with hepatitis C pharmacotherapies (with or without ribavirin), adding drugs, or switching treatment regimens in direct-acting antiviral–experienced patients with treatment-emergent NS3

Table 1: Selection Criteria	
	protease inhibitor resistance-associated variants of HCV (e.g., Q80K)
Comparator	Q1: Hepatitis C pharmacotherapies containing NS5B polymerase inhibitors (sofosbuvir, dasabuvir) in direct-acting antiviral–naive patients without NS5B resistance-associated variants of HCV Q2: Longer treatment duration with hepatitis C pharmacotherapies (with or without ribavirin), adding drugs, or switching treatment regimens in direct-acting antiviral–experienced patients without NS5B resistance-associated variants of HCV Q3: Hepatitis C pharmacotherapies containing NS3 protease inhibitors (simeprevir, grazoprevir, asunaprevir, paritaprevir) in direct-acting antiviral–naive patients without NS3 protease inhibitor resistance-associated variants of HCV (e.g., Q80K) Q4: Longer treatment duration with hepatitis C pharmacotherapies (with or without ribavirin), adding drugs, or switching treatment regimens in direct-acting antiviral–experienced patients without NS3 protease inhibitor resistance-associated variants (e.g., Q80K)
Outcomes	Treatment response (SVR12)
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), and non-randomized studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Studies on mixed populations (DAA naïve and DAA treatment-experienced patients) with outcome data not presented separately were excluded. Studies on treatment regimens with DAAs that are not approved in Canada were excluded.

Critical Appraisal of Individual Studies

The included reports on pooled analyses were critically appraised using the AMSTAR checklist[16] and the clinical studies were critically appraised using the Downs and Black checklist,[17] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 441 citations were identified in the literature search. Following screening of titles and abstracts, 381 citations were excluded and 60 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from hand search. Of these 61 potentially relevant articles, 48 publications were excluded for various reasons, while 13 publications met the inclusion criteria and were included in this report. These

were comprised of four reports[1,18-20] with pooled analyses of multiple studies and nine individual studies.[9,21-28] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included reports on pooled analysis and clinical studies are summarized below and details are available in Appendix 2, Table A1 and A2.

Reports on Pooled Analyses of Multiple Studies

The four included reports[1,18-20] with pooled analyses, were published between 2014 and 2016. Of these four reports, three reports[18-20] were from the USA, and one report[1] was from Belgium. Two reports[19,20] included patients with HCV infection with NS5B variants and of these reports, one report[20] was on DAA treatment naïve patients and one report[19] on DAA experienced patients. Two reports[1,19] included patients with HCV infection with NS3 variants and all were on DAA treatment naïve patients. Patient numbers (i.e. sum total of patients from the included studies) varied between 436 and 2007; however the numbers of patients evaluated in the analyses for the various resistance associated variants were fewer and not always clearly stated. Two reports[1,18] included patients infected with HCV GT1; one report[19] included patients infected with HCV GT1 to GT3; and one report[20] included patients infected with HCV GT1 to GT6. There was one report each for PRV[18] and SMV,[1] and two reports for SOF[19,20] containing regimens. SVR was evaluated in all the reports. Post treatment durations for assessment of SVR were 12 weeks, 24 weeks or weren't stated.

Clinical Studies

The nine included studies.[9,21-28] were published between 2013 and 2016. Of these nine studies, three studies[22,23,25] were international, four studies[9,18,21,26] were from the USA, one study[28] was from France and one study[24] was from Japan. Three studies[9,22,25] were RCTs, which included analysis of subgroups with and without RAVs, it was however, unclear if the subgroups had been determined a priori. One study,[26] was a retrospective analysis of a subgroup of patients from a RCT, to determine if response was impacted by the RAV status of patients. Five studies[21,23,24,27,28] were prospective single treatment arm studies, which included analyses of subgroups with and without RAVs, it was however, unclear if the subgroups had been determined a priori. Of these five studies, two studies[24,28] were stated to have "real world" setting, involving patients from clinical practice.

Of the two studies[9,28] including HCV patients and assessing treatment response with respect to both NS5B or NS3 variants, one study[9] was on HCV GT1 infected and DAA treatment naïve patients who were being treated with regimens containing PRV with and without DSV; and one study[28] was on HCV GT1b infected and DAA treatment experienced patients who were being retreated with SOF and SMV containing regimens. One study,[21] assessing treatment response with respect to NS5B variants, was on HCV GT1 infected and DAA treatment experienced patients who were being retreated with SOF containing regimens. Of the six studies[22-27] on HCV patients and assessing treatment response with respect to NS3 variants, four studies[22,25-27] were on DAA treatment naïve patients and two studies[23,24] were on DAA treatment experienced patients. Of the four studies,[22,25-27] two studies[22,26] included HCV GT1 infected patients, one study[27] included HCV GT1b infected patients and one study[25] included HCV GT1, GT4,or GT6 infected patients. For the patients with NS3 variants and who were DAA treatment naïve, the treatment regimens included ASV in two studies,[26,27] GZR in one study,[25] and SMV in one

study.[22] For the patients with NS3 variants and who were DAA treatment experienced, the treatment regimens included GZR in one study,[23] and SMV in one study. SVR was evaluated in all the reports. Post-treatment durations for assessment of SVR were 12 weeks, 24 weeks or weren't stated.

Summary of Critical Appraisal

Critical appraisal of the included reports on pooled analysis and clinical studies is summarized below and details are available in Appendix 3, Tables A3 and A4.

Reports on Pooled Analyses of Multiple Studies

In all the four reports[1,18-20] with pooled analyses, the objectives were clearly stated. In all the reports it was unclear if a systematic review of literature had been conducted and justification for the inclusion of the selected studies was not provided, details of article selection, data extraction, and characteristics of the individual studies were lacking. It was unclear if quality of the included studies was assessed, publication bias was explored or if pooling was appropriate. All the studies were funded by industry.

Clinical Studies

All studies had clearly stated objectives. The objectives in all the included studies were to assess efficacy of one or more treatment regimen and were not designed to assess the effects of NS5B or NS3 variants on outcomes. The included studies presented analyses of subgroups with and without these variants but it was unclear if the subgroup analyses had been preplanned, hence the possibility of data dredging cannot be ruled out. Sample size and power determinations for assessing the effects of RAVs were not presented, unclear, or if presented were not for the purpose of determining differences between groups of patients with and without RAVs. Generalizability of the study findings were limited as sample sizes were small, and the numbers of patients with RAVs were often small compared to the numbers of patients without RAVs.

Study including NS5B variants:
In one included study[21] the inclusion criteria was stated, the exclusion criteria was not explicitly stated, patient characteristics, interventions and outcomes were described. Some of the authors had industry association.

Studies including NS5B and NS3 variants:
Two studies[9,28] on HCV infected patients, included NS5B and NS3 variants. In one study,[28] the inclusion and exclusion criteria, patient characteristics, interventions and outcomes were described. Some of the authors had industry association. In one study,[9] the intervention and outcome was described and the inclusion and exclusion criteria, and patient characteristics were not described. One study[9] was funded by industry and the authors had industry association and in one study[28] some authors had industry association; the funding source was unclear

Studies including NS3 variants:

Six studies[22-27] on HCV infected patients included NS3 variants. The inclusion and exclusion criteria was presented in all studies except for one study.[26] Patient characteristics, interventions

and outcomes were presented in all studies. Conflict of interest disclosures were provided in all six studies[22-27] and all or some of the authors had industry association and the studies were funded by industry.

Summary of Findings

What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS5B inhibitors in direct-acting antiviral–naive patients infected with NS5B resistance-associated variants of hepatitis C virus?

Findings are summarized below and details are provided in Appendix 4, Tables A5 and A6.

Pooled Analysis

A pooled analysis by Svarovskaia et al.[20] of nine studies on SOF-containing treatment regimens and involving 1645 patients with HCV (GT1 to GT6) infection and for whom sequencing data were available showed that of the 38 patients with NS5B RAVs, 35 (92%) patients achieved SVR. The authors stated that this SVR rate was comparable with the SVR rate among patients without known NS5B RAVs and to the overall SVR rate across all studies.

Single study analysis

Analysis from one study by Krishnan et al.[9] on treatment regimens with PRV and ritovavir (RTV) in combination with DSV, OMV or both and involving patients with HCV GT1, showed that of the seven patients with S556G NS5B RAV seven (100%) achieved SVR24 and of the 239 patients without S556G RAV, 220 (92%) achieved SVR24 (P = 1.0).

What is the clinical effectiveness of hepatitis C pharmacotherapies in direct-acting antiviral–experienced patients infected with treatment-emergent NS5B resistance-associated variants of hepatitis C virus?

Findings are summarized below and details are provided in Appendix 4, Tables A5 and A6.

Pooled Analysis

A pooled analysis by Svarovskaia et al.[19] included 23 HCV GT1 infected patients with either L159F or V321A NS5B variants and with virologic failure with prior SOF or SOF+LDV containing treatments. These 23 patients were when retreated with SOF+pegylated interferon with ribavirin (PR) or SOF+ribavirin (R), and 18 (78%) patients achieved SVR. This SVR rate was comparable to the SVR rate of 78% (382/490) observed in patients without L159F or V321A variants.

Single study analysis

Hézode et al.[28] analyzed 16 patients with HCV GT1 or GT 4 infection who had failed DCV containing regimens and were retreated with SOF+SMV containing regimens. Of the 16 patients, 14 achieved SVR12 and three of these patients had NS5B RAVs. Of the two patients who did not achieve SVR12, none had NS5B RAVs.

Analysis from one study by Wilson et al.[21] on treatment regimens with SOF+LDV and involving 34 patients with HCV GT1 infection who had failed treatment with SOF+LDV in combination with NS5B or NS3 inhibitors, showed that 1 patient had both NS5B and NS5A RAVs and achieved SVR12 and five patients had no NS5B or NS5A RAVs and all five patients achieved SVR12. The remaining 29 patients had NS5A RAVs which are not relevant for this report.

What is the clinical effectiveness of hepatitis C pharmacotherapies containing NS3 protease inhibitors in direct-acting antiviral–naive patients infected with NS3 protease inhibitor resistance-associated variants of hepatitis C virus at baseline?

Findings are summarized below and details are provided in Appendix 4, Tables A5 and A6.

Pooled Analysis

Two relevant reports[1,18] with pooled analyses were identified (Table 2). One report[18] on PRV containing regimens for the treatment of patients with HCV GT1b infection, showed that the SVR rates were comparable between patients with and without NS3 variants (Table 2). One report[1] on SMV containing regimens for treatment of patients with HCV GT1a infection, showed that the SVR rates were lower in patients with NS3 variants compared to those without the variant (Table 2).

Table 2: Pooled Analyses: Results with respect to NS3 RAVs

Study (with pooled analyses)	No. of Studies Included	Population	Treatment regimen, Outcome	Percentage (ratio) of patients achieving SVR	
				For patients with NS3 RAV	For patients without NS3 RAV
Krishnan,[18] 2016, USA	Study 1	GT1b (non-cirrhotic)	PRV+OMV+R, SVR24	88 (7/8) to 100 (19/19)	98 (50/51) to 100 (62/62)
	Study 2	GT1b (cirrhotic and non-cirrhotic)		95 (37/39) to 100 (13/13)	96 (152/158) to 98 (260/266)
Lenz,[1] 2015, Belgium	2	GT1a (naïve or interferon regimen experienced)	SMV+PR, SVR12	58.3 (49/84)	83.6 (138/165)

GT = genotype, OMV = ombitasvir, P = pegylated interferon , PR = pegylated interferon and ribavirin, PRV = paritaprevir, RAV = resistance associated variant, SMV = simeprevir, SVR = sustained virological response

Single Study Analysis

Five relevant studies,[9,22,25-27] reporting on various treatment regimens for patients with HCV infection with NS3 variants and who were DAA treatment naïve, were identified (Table 3). Two studies[26,27] on ASV containing regimens for treatment of patients with HCV GT1 infection showed that the SVR rates were comparable between patients with and without NS3 variants (Table 3). One study[9] on PRV containing regimens for the treatment of patients with HCV GT1 showed that that the SVR rates were lower in patients with NS3 variants compared to those without the variant (Table 3). One study[25] on GZR containing for treatment of patients with HCV GT1 and GT4 infection, showed that the SVR rates were higher for GT1a infected patients with NS3 variants compared to those without NS3 variants and the SVR rates were comparable for GT1b or GT4 infected patients with or without NS3 variants (Table 3). One study[22] on SMV-containing regimens (SMV+DCV with or without ribavirin) for the treatment of patients with HCV GT1b infection, showed that the SVR rates were comparable between patients with and without NS3 variants.

Table 3: Single Study Analysis: Results for treatment regimens with ASV, PRV, SMV, or GRZ with respect to NS3 RAVs

Study	Study type	Population	Treatment regimen, Outcome	% (ratio) of patients achieving SVR	
				For patients with NS3 RAV	For patients without NS3 RAV
Karino,[27] 2013, Japan	Prospective, phase 2, open label, single arm (N = 6 [for this data set: 3 with NS3 polymorphism and 3 with no polymorphism])	GT1b (non-responders or ineligible/ intolerant to PR)	ASV+DCV, SVR24	100 (3/3)	100 (3/3)
McPhee,[26] 2013, USA	Analysis of one group from an open label RCT, (N = 11)	GT1 (PR experienced [null responders])	ASV+DCV, SVR24 or SVR48	25 (1/4)	25 (1/4)
Krishnan,[9] 2015, USA (AVIATOR)	Analysis of open label, phase 2, RCT with 14 arms, (N =571, not all included in the analysis)	GT1 (naïve and PR experienced [null responders])	Dual or triple therapy with PRV/RTV with OMV, DSV or both (and with or without R); SVR24	88 (78/89) (with Q80K)	94 (122/130) (without Q80K)

Table 3: Single Study Analysis: Results for treatment regimens with ASV, PRV, SMV, or GRZ with respect to NS3 RAVs

Study	Study type	Population	Treatment regimen, Outcome	% (ratio) of patients achieving SVR	
				For patients with NS3 RAV	For patients without NS3 RAV
Zeuzem,[25] 2015, International (C-EDGE)	Analysis of RCT (blinded and then open label) (N= 421, not all included in the analysis)	GT1, GT4, GT6 (predominantly GT1) (naïve)	GZR+EBR, SVR12	97 83/86) (GT1a), 96 (24/25) (GT1b), 100 (7/7) (GT4), 78 (7/9) (GT6),	89 (58/65) (GT1a), 100 (104/104) (GT1b), 100 (11/11) (GT4), NA (GT6)
Zeuzem,[22] 2016, USA, Europe (LEAGUE-1)	Analysis of open label, phase 2, RCT (N = 147 for GT1b)	GT1b (naïve and PR experienced [null responders])	SMV+DCV with or without R, SVR12	80 (24/30)	82 (89/109)

ASV = asunaprevir, DCV = daclatasvir, DSV = dasabuvir, EBR = elbasvir, GT = genotype, GZR = grazoprevir, OMV = ombitasvir, PR = pegylated interferon and ribavirin, PRV = paritaprevir, R = ribavirin, RAV = resistance associated variant, RCT = randomized controlled trial, RTV = ritonavir, SMV = simeprevir, SVR = sustained virological response

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What is the clinical effectiveness of hepatitis C pharmacotherapies in direct-acting antiviral–experienced patients infected with treatment-emergent NS3 protease inhibitor resistance-associated variants of hepatitis C virus?

Single Study Analysis

Three included studies[23,24,28] reporting on GZR or SMV containing regimens for retreatment of patients with HCV infection with NS3 variants and who were DAA treatment experienced were identified (Table 4). One study[23] on a regimen containing GZR for retreatment of patients infected with GT1 and who had failed a prior DAA containing regimen showed that the SVR rates were lower for patients with NS3 variants compared to those without the variants (Table 5). One study[28] on a regimen containing SMV for treatment of patients with HCV GT1 or GT4 infections and who were DAA treatment experienced showed that the SVR rates were lower for patients with NS3 variants compared to those without the variants. One study[24] on a regimen containing SMV for retreatment of patients with HCV GT1b infections and who were DAA treatment experienced, showed that the SVR rates were higher for patients with NS3 variants compared to those without the variants.

Table 4: Results for treatment regimens containing GZR or SMV for patients with NS3 RAVs who were DAA treatment experienced

Study	Study type	Population	Treatment regimen, Outcome	% of patients achieving SVR	
				For patients with NS3 RAV	For patients without NS3 RAV
Buti,[23] 2015, International, (C-SALVAGE)	Prospective, phase 2, open label, study, (N = 79)	GT1 (who had failed PR treatment combined with BOC, TVR, or SMV)	GRZ+EBR+R, SVR12 and SVR24	91% (31/34)	100% (45/45)
Hezode,[28] 2016, France	"Real-life" pilot study, (N = 16)	GT1 and GT4 who had failed PR treatment combined with DCV or DCV+ASV	SOF+SMV, SVR12	75 (6/8)	100 (8/8)
Ogawa,[24] 2015, Japan	Prospective study (N = 11 relevant for this report)	GT1b who had failed TVR treatment (also with respect to prior PR: naïve and treatment experienced),	SMV+PR, SVR12	100 (1/1) (PR naïve); 100 (1/1) (partial PR responders)	75 (3/4) (PR naïve or relapser); 80 (4/5) (partial PR responders)

ASV = asunaprevir, BOC = boceprevir, EBR = elbasvir, GT = genotype, GZR = grazoprevir, NR = not reported, PR = pegylated interferon and ribavirin, R = ribavirin, RAV = resistance associated variant, SOF = sofobuvir, SMV = simeprevir, SVR = sustained virological response, TVR = telaprevir

Limitations

Some of the studies used population sequencing, which has the potential of missing minor variants and underestimating the frequency of occurrence of potentially relevant variants.

Many of the included studies were post hoc analyses of previously conducted studies and the analyses included only patients for whom sequencing data were available. Hence it is unclear, the extent to which the results would be impacted had it been possible to get sequencing data for all patients and to include all patients in the analysis. Furthermore details of patient characteristics of the population analyzed were not always presented, hence, it was unclear if there were differences in the patient groups with or without sequencing data. The reports on pooled analyses with multiple studies did not appear to have included a systematic approach for selecting studies hence bias in selecting studies cannot be ruled out.

The prevalence of baseline polymorphisms were often low, hence definitive conclusions on their possible impact on the outcomes are not possible. The majority of the studies were on GT1

patients. Information on the other genotypes was sparse. Comparison across different studies was difficult as the treatment regimens varied. There was overlap in the studies in the two reports[19,20] with pooled analyses regarding SOF containing treatment regimens.

None of the studies were conducted in Canada, hence generalizability to the Canadian setting is unclear.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Thirteen relevant articles were included and these were comprised of four reports[1,18-20] with pooled analyses of multiple studies and nine studies.[9,21-28].

One report[20] of a pooled analysis, showed that in DAA naïve patients who were infected with HCV GT1 to GT6, the SVR rate with SOF containing treatment regimens were comparable between patients with and without NS5B RAVs. One study[9] showed that in DAA naïve patients who were infected with HCV GT1, the SVR rate with PRV containing treatment regimens were comparable between patients with and without NS5B RAVs.

One report[19] of a pooled analysis showed that, in DAA experienced patients who were infected with HCV GT1, the SVR rate for retreatment with SOF containing regimens were comparable between patients with and without NS5B RAVs. Two studies[21,28] showed that in DAA experienced patients with HCV GT1 infection, all patients with NS5B achieved SVR when retreated with SOF containing regimens, however it needs to be noted there were small numbers of patients with NS5B in these two studies.

One report[18] on a pooled analysis showed that, in DAA naïve patients who were infected with HCV GT1b, the SVR rates with PRV containing regimens were comparable between patients with and without NS3 RAVs. One report[1] on pooled analysis showed that, in DAA naïve patients who were infected with HCV GT1a, the SVR rates with SMV containing regimens were lower with NS3 present compared to NS3 absent. In DAA naïve patients who were infected with HCV GT1, the SVR rates with PRV,[9] GZR[25], or SMV[22] containing regimens were comparable for patients with and without NS3. The SVR rates with SMV in the pooled analysis[1] and in the single study[22] differed as the pooled analysis assessed SMV in combination with PR and the single study assessed SMV in combination with DCV.

One study[23] showed, that in DAA experienced patients who were infected with HCV GT1, the SVR rate for retreatment with GZR was 91% in patients with NS3 and was 96% for the total patient population; the SVR rates for retreatment with SMV containing regimens were inconsistent.[24,28]

Howe et al.[29] mentioned that not all baseline or emergent HCV protease variants result in clinically meaningful drug resistance and that it is important to distinguish between RAVs and therapeutically inconsequential polymorphisms before considering RAV testing.

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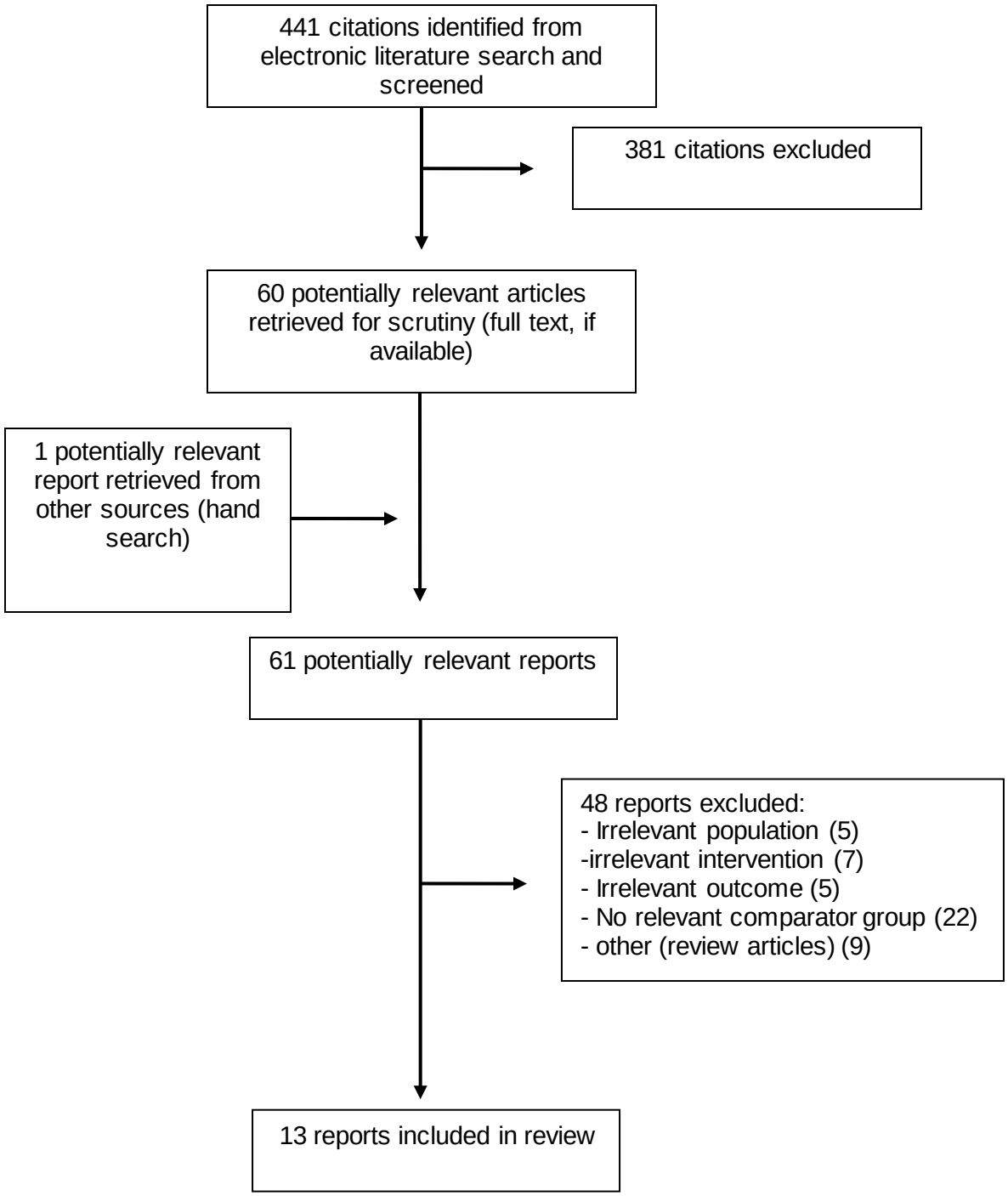
ABBREVIATIONS

ASV	Asunaprevir
BL	baseline
CI	Confidence interval
DAA	Direct-acting antiviral agent
DCV	Daclatasvir
DSV	Dasabuvir
EBR	Elbasvir
GZR	Grazoprevir
GT	genotype
HCV	Hepatitis C virus
IU	International units
LDV	Ledipasvir
LLOQ	lower limit of quantitation
NA	not applicable
NR	not reported
OMV	Ombitasvir
OR	Odds ratio
P	pegylated interferon
PCR	Polymerase chain reaction
PEG	Pegylated
PR	pegylated interferon plus ribavirin
PRV	paritaprevir
RAV	Resistance-associated variant
RBV (or R)	Ribavirin
RCT	randomized controlled trial
RNA	Ribonucleic acid
RTV	Ritonavir
SD	Standard deviation
SE	Shannon entropy
SMV	Simeprevir
SOF	Sofosbuvir
SVR	Sustained virological response
SVR12	Sustained virological response at post-treatment week 12
SVR24	Sustained virological response at post-treatment week 24
TVR	Telaprevir
USA	United States of America

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Reports with Pooled Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics[a]	Comparisons[a]	Clinical Outcomes[a]
Krishnan,[18] 2016, USA	Separate analysis of two RCTs ([M12-536, also NCT01672983] and [GIFT-1 also NCT01672983]) for SVR data Prevalence data taken from 7 studies (Sequencing method: population sequencing or deep sequencing)	Patients with HCV GT-1b infection. M12-536 N = 73 noncirrhotic patients GIFT-1 N = 363 (321 noncirrhotic patients and 42 cirrhotic patients) Age (years): NR Male (%): NR HCV RNA levels: NR	PRV+OMV combination regimens with R M12-536 Once daily 25 mg OMVplus prv/r at 100/1000 mg or 150/100 mg for 12 or 24 weeks (4 groups) GIFT-1 Once daily fixed combination of OMV/PRV/R 25 mg/ 150 mg/ 100 mg (termed 2D regimen) for 12 weeks (2 groups)	SVR24
Lenz,[1] 2015, Belgium	Pooled analysis with 5 studies (phase 2b or phase 3; PILLAR, ASPIRE, QUEST-1, QUEST-2, and PROMISE) 5 studies used for prevalence data and 2 studies used for SVR data with respect to baseline RAV status	Patients with HCV GT-1 (GT1a, GTb, and non-GT1a/1b) infection. Patients were naïve or treatment (interferon based regimen) experienced N =2007 (with sequence analysis)	SMV in combination with PR or placebo in combination with PR SMV (75 mg, 100 mg, or 150 mg) once daily in combination with PR	SVR12

Table A1: Characteristics of Included Reports with Pooled Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics[a]	Comparisons[a]	Clinical Outcomes[a]
	(Sequencing method: population sequencing)			
Svarovskaia,[20] 2014, USA	Pooled analysis with 9 studies (5 phase 2 and 4 phase 3) (study names: QUANTUM, P7977-0221, PROTON, ELECTRON, ATOMIC, POSITRON, FUSION, NEUTRINO, FISSION) (Sequencing method: population sequencing and deep sequencing)	Patients with HCV GT-1 to 6 infection 6 studies included treatment naïve patients, 1 study included interferon intolerant patients, 1 study included patients who failed interferon, and 1 study included a mixed population (treatment naïve patients and treatment experienced null responders) N = 1645 with sequencing data available	SOF containing regimens SOF alone, SOF/R or SOF/P/R Treatment duration varied between 4 and 24 weeks	SVR
Svarovskaia,[19] 2016, USA	Pooled analysis with 13 studies (NEUTRINO, FISSION, POSITRON, FUSION, VALENCE, PHOTON-1, PHOTON-2,P7977-2025 [liver pretransplantation study], LONESTAR, ELECTRON, ION1, ION2, and ION3) (Sequencing	Patients with HVC GT-1 to 3 infection 1611 patients with baseline sequence data available (from studies on SOF containing regimens); 1470 patients with baseline sequence data available (from studies on SOF/LDV containing regimens) N =23 patients (from these studies) with virologic failure had L159 F or V321A variants and were retreated.	Retreatment with SOF+PR for 12 weeks or SOF+R for 24 weeks	SVR

Table A1: Characteristics of Included Reports with Pooled Analyses				
First Author, Publication Year, Country	**Types and numbers of primary studies included**	**Population Characteristics[a]**	**Comparisons[a]**	**Clinical Outcomes[a]**
	method: deep sequencing)	Age (years): NR Male (%): NR HCV RNA levels: NR		

BL = baseline resistance, GT = genotype, HCV = hepatitis C, NR = not reported, P = pegylated interferon, PR = pegylated interferon plus ribavirin, RCT = randomized controlled trial, SMV = simeprevir, SVR = sustained virologic response, TVR = telaprevir
[a]Only information relevant for this report are presented

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics[a]**	**Intervention(s)[a]**	**Comparator(s)[a]**	**Clinical Outcomes[a]**
Buti,[23] 2015, International: USA, Europe, Israel, (C-SALVAGE)	Prospective open-label, phase 2 (Population sequencing)	Adults with HCV GT-1 infection who had failed ≥ 4 weeks of treatment with PR combined with BOC, TVR or SMV. N =79 Age (years): NR Male (%): NR Mean HCV RNA: 10, 000 IU/mL	Retreatment with GRZ+EBR GRZ: 100 mg once daily, EBR: 50 mg once daily, RBV: 800 to 1400 mg (based on weight) twice daily Treatment duration: 12 weeks	NA	SVR12, SVR24
Hézode,[28] 2016, France	Prospective study on patients who had failed to achieve an SVR in phase 2 or 3 trials. "Real-life" pilot study.	Patients with chronic HCV who had failed prior treatment with DCV+PR or DCV+ASV+PR. Patients had severe fibrosis or compensated cirrhosis N = 16 (11 GT1a, 3 GT1b, and 2 GT4) Age(mean ± SD) (years): 54.9 ±	Retreatment with SOF+SMV SOF 400 mg capsule once daily, SMV 150 mg capsule once daily Treatment duration 12 weeks	NA	SVR12

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
		7.8 Male (%): 81 HCV RNA (Log_{10} IU/mL): 6.14			
Karino,[27] 2013, Japan	Prospective study: Phase 2, open label, 1 arm (patients enrolled in Japan) (Population sequencing)	Adult patients with HCV GT1b, who were non responders or ineligible/ intolerant to prior IFN+RBV treatment N =21+22 Age (years): 20 to 75 (inclusion criteria) Male (%); NR HCV RNA: $\geq 10^5$ IU/ ml (inc criteria) (Patient details not reported but available in another publication)	DCV+ASV Dose: 60 mg DCV once daily with 100 mg ASV twice daily, for 24 weeks.	NA	SVR
Krishnan,[9] 2015, USA	RCT, open label, phase 2 with 14 arms (AVIATOR [M11-652, NCT01464827])	Patients with HCV GT1 infection and without cirrhosis and who were treatment naïve or prior null responders to PR N = 571 Age (years): NR Male (%): NR	PRV/RTV, OMV, DSV, R. (14 treatment arms. Various 2D or 3D regimens of PRV/RTV with OMV or DSV or both. Dose: PRV (100 mg, 150 mg, or 200 mg) with 100 mg RTV once daily, 25 mg OMV once daily, and 400 mg DSV twice daily Treatment duration was 8, 12 or 24 weeks		SVR24 (HCV RNA level below LLOQ (25 IU/mL) at 24 weeks post-treatment

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
		HCV RNA: NR			
McPhee,[26] 2013, USA	Retrospective analysis of one group from an open label RCT	Patients with HCV GT1 infection who were null responders to prior therapy with PR N = 11 (9 GT1a, 2 GT1b) Age (years): NR Male (%): NR Viral load: NR	Dual therapy with ASV+DCV 600 mg ASV twice daily, 60 mg DCV once daily. Treatment duration was 24 weeks	NA	SVR
Ogawa,[24] 2015, Japan	Prospective study with analysis of a group (patients who had failed prior TVR therapy) selected from real world settings	Patients with GT1b with prior TVR treatment failure N = 20 (response to prior PR treatment: 4 naïve, 1 relapse, 6 partial response, and 9 null response) Age (median [first-third quartile) (years): 64 (57 to 70) Male (%): 60 HCV RNA level (log_{10} IU/mL): 6.2	SMV+PR SMV (100 mg) once daily, P-2a (180 µg) or P-2b (1.5 µg/kg) once daily by subcutaneous injections, R daily dose 600 to 1000 mg based on weight.	NA	SVR12
Wilson,[21] 2016, USA	Prospective study. Phase 2a, open label study (NIAID SYNERGY	Patients infected with HCV GT1 infection, who had relapsed after 6 weeks on	Retreatment with LDV/SOF Treatment duration 12	NA	SVR12

Table A2: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics[a]**	**Intervention(s)[a]**	**Comparator(s)[a]**	**Clinical Outcomes[a]**
	[NCT01805882]). This study was conducted as a separate arm of the NIAID SYNERGY study (Sequencing method: population sequencing)	LDV/SOF plus GS-9669 (nonnucleoside NS5B inhibitor); 4 weeks on LDV/SOF plus GS09451 (a NS3 protease inhibitor); or 4 weeks on LDV/SOF plus GS-9669 and GS-9451. N = 34 (26 GT1a, 8 GT1b; majority were African American) Age (mean ± SD) (years): 58.9 ± 7.5 Male (%): 82.3 Proportion (%) with HCV RNA >800,000 IU/mL: 61.8	weeks		
Zeumen,[22] 2016, USA, Europe (LEAUGE-1)	RCT (phase 2), open label, 2 arm (1:1), Details of patient enrollment and study centers not reported.	Adults with HCV GT1a or GT1b, who were treatment naïve or non-responders to prior PEG-INF+RBV treatment. However, only GT 1b group had data relevant for this report N= 168 (6 groups by GT, prior treatment & current	(1)DCV+SMV Dose: DCV (30 mg +SMV (150 mg) administered orally once daily, for 12 weeks	(2)DCV+SMV+RBV Dose: DCV (30 mg +SMV (150 mg) + weight based RBV, administered orally once daily, for 12 weeks	SVR12 (HCV RNA <LLOQ detectable or undetectable at post-treatment week 12)

Table A2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics[a]	Intervention(s)[a]	Comparator(s)[a]	Clinical Outcomes[a]
		treatment. GT1b: 147, GT 1a: 21) Age range in GT 1b groups (median[range]): 53(28 to 81 and 59 (20 to 78) Male (%) in GT 1b: 42 to 52 Mean HCV RNA (log_{10} IU/ml): 6.2 to 6.4			
Zeumen,[25] 2015, USA, Europe, Australia, Scandanavia, Asia. (C-EDGE)	RCT, blinded and later open label, 2 arm (3:1), multicenter (patients enrolled from centers in USA, Europe, Australia, Scandanavia and Asia)	Adults with HCV GT1, GT4 or GT6 infection; treatment naïve N = 421 (316/105) Age (mean±SD) (years): 52.6± 11.2 (52.2±11.1/ 53.8±11.2) Male (%): 54 (54/53) HCV RNA (geometric mean) (log_{10} IU/ml): 6.4 (6.4/6.4) GT 1a (%): 50 (50/42) GT1b (%): 41 (42/38) GT 4 (%): 6(6/8) GT 6 (%): 3(3/3)	(1) Immediate therapy with GZR+EBR Dose: fixed dose combination of GZR (100 mg +EBR (50 mg) administered orally once daily, for 12 weeks	(2)Placebo (Deferred therapy with GZR+EBR [deferred for 4 weeks])	SVR12 (Primary outcome was SVR12 in the immediate therapy group) SVR12 defined as unquantifiable HCV RNA 12 weeks after treatment

ASV = asunaprevir, BOC = boceprevir, DSV = dasabuvir, EBR = elbasvir, GRZ = grazoprevir, GT = genotype, HCV = hepatitis C virus, LLOQ = lower limit of quantitation, NA = not applicable, NIAID = National Institute of Allergy and Infectious Disases, NR = not reported, OMV = ombitasvir, P = pegylated interferon, PR = pegylated interferon plus ribavirin, R = ribavirin, RCT = randomized controlled trial, RNA = ribonucleic acid, RTV = ritonavir, SMV = simeprevir, SVR = sustained virologic response, TVR = telaprevir, VF = virologic failure

[a]Only information relevant for this report are presented

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Reports with Pooled Analyses using AMSTAR checklist16

Strengths	Limitations
Krishnan,[18] 2016, USA	
• Objectives were clearly stated. • Conflict of interest was declared. Authors have industry association	• Systematic literature search of relevant studies does not appear to have been undertaken • Details of article selection and data extraction were lacking • Characteristics of the individual studies were not presented • Quality assessment of the included studies was not presented. • No pooling of data • Publication bias was not explored • Study funded by industry
Lenz,[1] 2015, Belgium	
• Objectives were clearly stated. • Characteristics of the individual studies were presented but lacked details • Conflict of interest was declared. Authors were employees of industry	• Systematic literature search of relevant studies does not appear to have been undertaken • Details of article selection and data extraction were lacking • Quality assessment of the included studies was not presented. • Unclear if pooling was appropriate • Publication bias was not explored • Study funded by industry
Svarovskaia,[20] 2014, USA	
• Objectives were clearly stated. • Characteristics of the individual studies were presented but lacked details • Authors submitted conflicts of interest disclosure forms. Most of the authors were employees of industry	• Systematic literature search of relevant studies does not appear to have been undertaken • Details of article selection and data extraction were lacking • Quality assessment of the included studies was not presented. • Unclear if pooling was appropriate • Publication bias was not explored • Study funded by industry
Svarovskaia,[19] 2016, USA	
• Objectives were clearly stated. • Authors disclosed conflicts of interest. Most of the authors were employees of industry or had association with industry.	• Systematic literature search of relevant studies does not appear to have been undertaken • Details of article selection and data extraction were lacking • Characteristics of the individual studies were not presented • Quality assessment of the included studies was not presented. • Unclear if pooling was appropriate • Publication bias was not explored • Study funded by industry

Table A4: Strengths and Limitations of Clniical Studies using Downs and Black Checklist17	
Strengths	**Limitations**
Buti,[23] 2015, International: USA, Europe, Israel, (C-SALVAGE)	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Intervention and outcomes were described • None lost to follow up • Authors provided disclosures of conflicts of interest. All had association with industry	• Details of patient characteristics were not presented • Non-randomized study. Single arm study. • Unclear if sample size and power calculations were conducted • *P* values were not presented • Study funded by industry and all authors were associated with industry • Generalizability unclear
Hézode,[28] 2016, France	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described • Study was mentioned to be a real-life study • Disclosures were provided by four of the 11 authors and they had industry association	• Not randomized. Study was on retreatment of some patients who had participated in phase 2 and 3 studies and had failed treatment • Unclear if sample size and power calculations were conducted • *P* values not provided • Generalizability limited to the study population (N = 16; patients had severe fibrosis or compensated cirrhosis)
Karino,[27] 2013, Japan	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described but details were lacking • Disclosures were provided by the authors. Authors have industry association	• Not randomized, open label,1-arm study • Unclear if sample size and power calculations were conducted • High discontinuation rate (14%) • *P* values not provided • Study was funded by industry • Generalizability unclear
Krishnan,[9] 2015, USA	
• Objectives were clearly stated. • Interventions and outcomes were described • *P* values were provided • Disclosures were provided by the authors. Authors have industry association	• Post hoc analysis of a RCT • Inclusion and exclusion criteria were not explicitly stated. However details of the RCT are likely to be described in other publications. • Details of patient characteristics were not presented. • Unclear if sample size and power calculations were conducted • Study was funded by industry • Generalizability unclear
McPhee,[26] 2013, USA	
• Objectives were clearly stated • Intervention and outcomes were described	• Analysis of one group of a RCT • Inclusion and exclusion criteria were not stated. However details of the RCT are likely to be described in other publications. • Patient characteristics were not described • Unclear if sample size and power calculations were conducted • *P* values not provided • Generalizability limited to the study population. • All authors were employees of industry. • Study was funded by industry

Table A4: Strengths and Limitations of Clniical Studies using Downs and Black Checklist17	
Strengths	**Limitations**
Ogawa,[24] 2015, Japan	
• Objectives were clearly stated • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described • Disclosures were provided by the authors. One author had industry association, for the other authors it was stated that there were no conflicts of interest	• Not randomized. Study on a group of patients (N = 20) taken from a real life setting • Unclear if sample size and power calculations were conducted • *P* values not provided • Generalizability limited to the study population. However, patients were taken from a real world setting. • Study was funded by industry
Wilson,[21] 2016, USA	
• Objectives were clearly stated • Inclusion criteria were stated • Patient characteristics were described. Interventions and outcomes were described • Disclosures were provided by the authors. Of the 19 authors, 14 authors were stated to have no conflicts of interest and the remaining five authors were industry employees.	• Not randomized. Single arm open label study • Unclear if sample size and power calculations were conducted • *P* values not provided • Generalizability limited to the study population (N = 34, predominantly [82.4%] African Americans and predominantly [82.4%] male). • The research was supported in part by a collaborative research and development agreement between industry and non-industry organizations. However, the entities did not have a role in writing of the manuscript
Zeumen,[22] 2016, USA, Europe, (LEAUGE-1)	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized • Modified ITT analysis conducted (patients who received ≥ 1 dose of study medication were included in analysis) • Disclosures were provided by the authors. Authors have industry association	• The study focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • Not blinded • *P* values for the outcomes relevant for this report were not provided • Generalizability is limited to patients with HCV GT 1b who were treatment naïve or non-responders to prior PEG-INF+RBV treatment. • Study was funded by industry
Zeumen,[23] 2015, USA, Europe, Australia, Scandanavia, Asia (C-EDGE)	
• Objectives were clearly stated. • Inclusion and exclusion criteria were stated • Patient characteristics, interventions and outcomes were described. • Randomized using a central interactive voice response system and computer generated random allocation • Patients, clinical sites and sponsor personnel were blinded. Separate medical team monitoring virologic failure and SAE was unblinded • Sample size determination was mentioned • Disclosure forms were provided by the authors. Authors have industry association	• The study focus was different from the research question being addressed in this report hence randomization and sample size calculation do not apply for this research question. • *P* values for the outcomes relevant for this report were not provided • Unclear if ITT, however likely not an issue as lost to follow up & discontinuations were few. • Generalizable to some extent as this was a multinational study. However, generalizability is limited to cirrhotic and noncirrhotic treatment naïve adults with GT1, GT 4 or GT6. Also, generalizability is limited by the exclusion criteria of excluding patients with coinfections/comorbidities (such as decompensated liver disease, hepatocellular

Table A4: Strengths and Limitations of Clniical Studies using Downs and Black Checklist17	
Strengths	**Limitations**
	carcinoma, HIV, HBV infection) • Study was funded by industry

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings from Reports on Pooled Analyses

Main Study Findings and Author's Conclusions

Krishnan,[18] 2016, USA

Main Findings:

SVR with PRV and OMV containing regimens in patients (non-cirrhotic) with HCV GT-1b infection and with or without baseline RAVs in study M12-536

Target	Baseline variant	Proportion achieving SVR24 Ratio (%)[a]	
		With variant	With wild type
NS3	Y56F	24/25 (96)	45/ 45 (100
	Q80H/I/K/L/M	7/8 (88	62/ 62 (100)
	S122G/N/T	19/19 (100)	50/ 51 (98)

[a]Patients not achieving SVR due to non-virologic reason, (such as early discontinuations, missing SVR time point, etc.), were excluded from the analysis. Only patients with available sequences (N) were included in the analysis. Hence N is less than the number of patients enrolled in the study and differs by target.

SVR with PRV and OMV containing regimens in patients (non-cirrhotic) with HCV GT-1b infection and with or without baseline RAVs in study GIFT-1

Target	Baseline variant	Proportion achieving SVR24 Ratio (%)[a]	
		With variant	With wild type
NS3	T54S	13/13 (100)	294/303 (97
	V55I	1/1 (100)	305/314 (97)
	Y56F	13/116 (97)	188/194 (97)
	Q80 H/K/L/M/N/R	37/39 (95)	260/266 (98)
	S122 A/C/G/N/T/V	112/116 (97)	152/158 (96)
	D168E	3/3 (100)	299/308 (97)

[a]Patients not achieving SVR due to non-virologic reason, (such as early discontinuations, missing SVR time point, etc.), were excluded from the analysis. Only patients with available sequences (N) were included in the analysis. Hence N is less than the number of patients enrolled in the study and differs by target.

SVR with PRV and OMV containing regimens in patients (cirrhotic) with HCV GT-1b infection and with or without baseline RAVs in study GIFT-1

Target	Baseline variant	Proportion achieving SVR24 Ratio (%)[a]	
		With variant	With wild type
NS3	T54S	1/1 (100)	36/39 (92)
	Y56F	10/11 (91)	23/25 (92)
	Q80 H/K/L/M/N/R	4/4 (100)	28/31 (90)
	S122 A/C/G/N/T/V	15/18 (83	15/15 (100)
	D168E	1/1 (100)	36/39 (92)

[a]Patients not achieving SVR due to non-virologic reason, (such as early discontinuations, missing SVR time point, etc.), were excluded from the analysis. Only patients with available sequences (N) were included in the analysis. Hence N is less than the number of patients enrolled in the study and differs by target.

Prevalence of baseline polymorphism in NS3 in GT1b infected patients

Target	Baseline polymorphism	Prevalence Ratio (%)[a] in:	
		Japanese patients	Western patients
NS3	T54S	14/424 (3.3)	6/371 (1.6)
	V55A/I	1/424 (0.2)	4/371 (1.0)
	Y56F	153/424 (36.1)	124/371 (33.4)

Table A5: Summary of Findings from Reports on Pooled Analyses

Main Study Findings and Author's Conclusions

	Q80H/I/K/M/R	9/424 (2.1)	1/371 (0.3)
	Q80L	45/424 (10.6)	19/371 (5.1)
	S122A/C/D/I/N/R/T/V/Y	46/424 (10.9)	40/371 (10.8)
	S122G	111/424 (26.2	19/371 (5.1)
	A156T/V	-	2/371 (0.5)
	D168E	5/424 (1.2)	1/371 (0.3)

[a]Ratio indicates the number of patients with baseline variants divided by the total number of samples sequenced

Authors' Conclusions:

"In summary, Japanese GT1b-infected patients treated with paritaprevir/r and ombitasvir achieved high SVR rates. Certain NS3 and NS5A polymorphisms were detected at a higher prevalence in the Japanese population than in the western population. The impact of baseline RAVs on treatment outcome was limited to Y93H in NS5A; however, a majority of patients with this variant achieved SVR." Page 1112

Lenz,[1] 2015, Belgium

Main Findings:

SVR12 with SMV containing regimens in patients with HCV GT1a infection and with or without baseline RAVs (from QUEST-1 and QUEST-2 studies)

Baseline RAV status	Proportion achieving SVR12 Ratio (%)
With Q80K	49/84 (58.3)
Without Q80K	138/165 (83.6)

Prevalence of baseline Q80K polymorphism in HCV GT1 infected patients (from 5 studies)

Region	Prevalence		
	All GTs	GT1a[a]	GT1b
Overall	274/2007 (13.7)	269/911 (29.5)	5/1096 (0.5)
North America	185/538 (34.4)	185/385 (48.1)	0/153 (0)
South America	2/60 (3.3)	2/22 (9.1)	0/38 (0)
Europe	76/1254 (6.1)	73/377 (19.4)	3/877 (0.3)

[a]This group includes also 15 patients with non-GT1a/1b

Authors' Conclusions:

"In conclusion, simeprevir in combination with PR results in high SVR rates in HCV treatment-naïve and -experienced patients with HCV GT1 infection. The GT1a NS3 polymorphism Q80K has a modest impact on simeprevir activity in vitro, but might facilitate the emergence of additional mutations in patients treated with simeprevir/PR, especially in those with poor response to interferon, ultimately resulting in lower SVR in these patients when treated with simeprevir/PR. Treatment failure is typically associated with emerging high-level resistance mutations in the NS3 region that decline and become undetectable over time in many patients after treatment is stopped. Recent data suggest that emerging mutations do not preclude successful treatment outcome following subsequent treatment with DAAs with other mechanisms of action." Page 1013

Svarovskaia,[20] 2014, USA

Main Findings:

NS5B population sequencing data was available for 1645 patients (from 9 studies) with HCV (GT1 to 6) infection, who were treated with regimens containing SOF. The individual studies included one or more genotypes. Data, from these nine studies, were analyzed. Baseline RAVs were identified in 38 of these patients (two patients with N142T, 11 patients with L159F, and 25 patients with M289I/L). The RAVs: N96T, S282T, or L320F were not identified in any of the patients. Of the 38 patients with RAVs, 35 (92%) patients achieved SVR.

Table A5: Summary of Findings from Reports on Pooled Analyses

Main Study Findings and Author's Conclusions
This SVR rate is comparable with the overall SVR rate across all the studies and the SVR rate in patients without known RAVs (numerical values not reported). Of the three patients who did not achieve SVR, two patients had L159F RAV and one patient had M289I RAV **Authors' Conclusions:** "These data demonstrate a uniform susceptibility of subject-derived HCV to sofosbuvir, and also show that selection of sofosbuvir-resistant HCV is exceedingly rare and is associated with a significant reduction in viral fitness." Page 1666 "In summary, throughout 9 sofosbuvir phase 2 and 3 clinical trials, no antiviral resistance to sofosbuvir was detected either at baseline or in cases of virologic relapse except in 1 monotherapy subject. This favorable feature of sofosbuvir makes it an attractive option for future combination strategies against HCV." Page1672
Svarovskaia,[19] 2016, USA
Main Findings: **Outcome with SOF and SOF+LDV with or without P, R or PR in patients with HCV infection** "To investigate whether the emergence of L159F and V321A variants affected retreatment outcome with SOF regimens, 23 of the virologic failures across the SOF studies with either L159For V321A variants were retreated with either SOF + RBV + peginterferon for 12 weeks or with SOF + RBV for 24 weeks. Of these 23 patients, 18 (78%) achieved SVR following retreatment, which is similar the SVR rate of 78% (382 of 490 patients) observed in patients without L159F or V321A in the retreatment study, GS-US-334-0109." Page 1242 **Outcomes of retreatment with SOF+R with or without P in patients who had virologic failure with previous SOF containing regimens** "To investigate whether the emergence of L159F and V321A variants affected retreatment outcome with SOF regimens, 23 of the virologic failures across the SOF studies with either L159F or V321A variants were retreated with either SOF + RBV + peginterferon for 12 weeks or with SOF + RBV for 24 weeks. Of these 23 patients, 18 (78%) achieved SVR following retreatment, which is similar the SVR rate of 78% (382 of 490 patients) observed in patients without L159F or V321A in the retreatment study, GS-US-334-0109. All 5 patients from the retreatment study who experienced relapse had GT3a infection and L159F, and 1 also had emergent V321A from the parental study. At the time of retreatment failure, L159F was no longer detectable in any patient, and V321A was detected in 1 patient. In this patient, V321A was detected as a minor viral population, and the level was not enriched following retreatment." Page 1242 **Prevalence of L159 and V321A at baseline** "To evaluate pretreatment prevalence of L159F and V321A, baseline samples were deep sequenced from 1611 and 1470 patients who were subsequently treated with SOF-containing regimens in the SOF and LDV/SOF studies, respectively [.....]. The L159F variant was detected in only 0.6% of patients in the SOF studies and in 1.6% of patients in the LDV/SOF studies, while V321A was not detected in any patient at baseline. Of the patients with baseline L159F, the majority (32 of 33) had GT1b HCV, and 1 had GT1a HCV. The prevalence of baseline L159F was 7% in GT1b and <0.01% in GT1a, respectively. No baseline L159F was detected in patients with HCV GT2 or GT3 infection." Pages 1241-1242 **Authors' Conclusions:** "Deep-sequencing analysis confirmed that NS5B variants L159F and V321A emerged in a subset of patients treated with SOF at virologic failure. These variants had no impact on retreatment outcome with SOF, ribavirin, and pegylated interferon. Baseline L159F in genotype 1 did not affect the treatment outcome with LDV/SOF." Page 1240

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Buti,[23] 2015, International, (C-SALVAGE)

Main Findings

Outcomes with GRZ+EBR in patients with HCV GT-1 infection and with various baseline RAVs status and who had failed treatment with DAA containing regimen

RAV status	No. of patients	Outcome
NS3 variants	34	3 relapsed 31 (91%) achieved SVR12 and SVR24
Without NS3 variants	45	45 (100%) achieved SVR12 and SVR24
NS5A variants	8	2 relapsed 6 achieved SVR24
Both NS3 and NS5A variants	6	2 relapsed 4 achieved SVR24
High level GRZ resistance	4	1 relapsed 3 achieved SVR24
High level EBR resistance	5	2 relapsed 3 achieved SVR24
All patients (with and without RAVs)	79	3 relapsed 76 (96%) achieved SVR12 and SVR24

Authors' Conclusions

"Grazoprevir and elbasvir with ribavirin for 12 weeks maintained HCV suppression for at least 24 weeks posttherapy without late relapses. Baseline resistance-associated variants (RAVs) stably reappeared at relapse in all 3 patients with virologic failure." Page 32

"Unlike the transiently emergent NS3_A156T variant, NS5A_RAVs at relapse persisted for at least 24 weeks after cessation of therapy. If confirmed in larger numbers of patients, this finding could potentially have implications for the retreatment of the small number of patients who fail combination regimens containing an NS5A inhibitor" Page 35.

Hézode,[28] 2016, France

Main Findings

Outcomes with SOF+SMV in patients with HCV GT1 or GT4 infection

RAV status at baseline	No of patients with RAV	Outcome
Presence of ≥ 1 NS3 RAV	8	6 (75%) achieved SVR12, 2 did not achieve SVR12
Presence of ≥ 1 NS5B RAV	3	3 (100%) achieved SVR12,
Presence of ≥ 1 NS5A RAV	12	10 (83%) achieved SVR12, 2 did not achieve SVR12
Of the 16 patients in the study, 14 (88%) patients achieved SVR12 and the two who did not achieve SVR had both NS3 and NS5A RAVs present at baseline		

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Authors' Conclusions

"In conclusion, these real-life findings suggest high efficacy, good tolerance, and feasibility of a combination regimen of SOF and SIM in patients infected with chronic HCV GT 1 or 4 infection who have failed a previous DCV-based regimen. The study shows that patients who achieved rapid or early responses were more likely to achieve SVR than those achieving late responses. [……] These results support the concept of retreating NS5A inhibitor failures with SOF combined with SIM and provide a signal as to which patient profiles could require longer duration of therapy and or addition of RBV. Such patients may include those with cirrhosis and/or pre-existing RAVs" Page 1815

Karino,[27] 2013, Japan

Main Findings

Results, pertaining to SVR for HCV, GT-1b patients with and without NS5A and/or NS3 polymorphism present at baseline, were presented graphically and partially described in the text. Two groups of patients were assessed: (1) those who were ineligible, intolerant or both to PR treatment (N= 21) and (2) those who were non-responders to PR treatment (N = 21). Viral breakthrough and post treatment relapses were observed in the ineligible and/or intolerant group and not in the non-responder group.

Outcomes with ASV+DCV containing regimens in patients with HCV GT-1b infection

RAV status at baseline	No. of patients	Outcomes
With NS3 polymorphism	3	3 achieved SVR24
With NS5A polymorphism	7	1 relapse, 1 viral breakthrough, 1 discontinued, 4 achieved SVR24
With NS3 and NS5A polymorphism	9	1 relapse, 2 viral breakthrough 2 discontinued 4 achieved SVR24
Polymorphism not detected	3	1 discontinued by patient request but had SVR, 2 achieved SVR24

Authors' Conclusions

"A loose association with a baseline NS5A polymorphism on virologic outcome was observed; however, further data from larger studies are required." Page 653

Krishnan,[9] 2015, USA

Main Findings

Outcomes with PVR+RTV in combination with DSV or OMV or both and with or without R in patients with HCV GT-1 infection

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Target	Variant	Variant status at baseline	Proportion achieving SVR24 Ratio (%)[a]	P value[b]
NS3	Q80K	With variant	78/89 (88)	0.14
		Without variant	122/130 (94)	
	D168A	With variant	0/1 (0)	0.09
		Without variant	200/218 (92)	
NS5B	S556G	With variant	7/7 (100)	1.0
		Without variant	220/239 (92)	
	C316Y	With variant	1/2 (50)	0.15
		Without variant	226/244 (93)	

[a]Ratio indicates the number of patients achieving SVR24 divided by the total number of patients who had a sequence available. Patients not achieving SVR24 for non-virologic reasons (such as discontinuations or missing SVR24 data) were excluded from the analysis
[b]P values were calculated by the chi-square test

Prevalence of baseline polymorphism in NS3 or NS5B in GT1a infected patients

Target	Baseline polymorphism	Prevalence (%)[a]
NS3 (N = 230)	V36A	0.9
	V36L	1.3
	V36M	0.9
	Q80K	41
	Q80L	2.2
	D168A	0.4
NS5B (N = 258)	C316Y	0.8
	M414T	0.4
	A553G	0.4
	S556G	3.1
	S556N	0.4
	S556R	0.4

N = number of samples sequenced for that target
[a]Percentage of patients with the baseline polymorphism relative to the GT1a strain H77 reference sequence

Prevalence of baseline polymorphism in NS3 or NS5B in GT1b infected patients

Target	Baseline polymorphism	Prevalence (%)[a]
NS3 (N = 119)	None[b]	
NS5B (N = 125)	C316H	0.8
	C316K	0.8
	C316N	18.4
	C316W	0.8
	S368A	0.8
	M414L	0.8
	C445F	1.6
	S556G	16.0

N = number of samples sequenced for that target
[a]Percentage of patients with the baseline polymorphism relative to the GT1b strain Con1 reference sequence
[b]None: baseline polymorphisms were not detected at resistance-associated amino acid positions

Authors' Conclusions

"In conclusion, while RAVs in NS5A and NS5B were observed at baseline, they did not appear to affect treatment response, suggesting that this multitargeted HCV GT1 antiviral regimen affords a

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

high barrier to resistance." Page 5452

McPhee,[26] 2013, USA

Main Findings

Outcomes with ASV+DCV in patients with HCV GT-1 infection

RAV status at baseline	No. of patients	Outcomes
With NS3 polymorphism (Q80K or R155K)	4	1 relapse, 2 viral breakthrough, 1 (25%) achieved SVR48
With NS5A polymorphism	2	2 achieved SVR48
With NS3 and NS5A polymorphism	1	1 viral breakthrough
Polymorphism not detected	4	3 viral breakthrough, 1 (25%) achieved SVR48

Authors' Conclusions

"The treatment failure of daclatasvir and asunaprevir in HCV GT1a patients was associated with both NS5A and NS3 resistance variants in prior null responders. NS5A resistance variants persisted while NS3 resistance variants generally decayed, suggesting a higher relative fitness of NS5A variants." Page 902

Ogawa,[24] 2015, Japan

Main Findings

Outcomes with triple therapy with SMV+PR in patients with HCV GT-1b infection who had failed prior therapy with TVR (also PR naïve or experienced)

Patient group	RAV (for NS3) status at baseline[a]	No of patients	Outcome[b]
Naïve or relapsed on prior PR	With RAV (A156S)	1	1 achieved SVR12 (*had RAV with TVR tx)*
	Wildtype	4	3 achieved SVR12 *(1 had RAV, 1 had WT, and 1 NR with TVR tx)* 1 did not achieve SVR *(had WT with TVR tx)*
Partial response to prior PR	With RAV (A156S)	1	1 achieved SVR12 (*had RAV with TVR tx)*
	Wildtype	5	4 achieved SVR12 (*3 had RAV, 1 NR with TVR tx),* 1 did not achieve SVR (*had WT with TVR tx)*
Null response to prior PR	Wildtype	9	1 achieved SVR12 (*had RAV with TVR tx)* 8 did not achieve SVR12 *(6 had RAVs and 2 had WT with TVR tx)*

[a]Baseline i.e. at initiation of SMV containing regimen. Of note patients may or may not have had RAVs (for NS3) at time of relapse or viral breakthrough with prior TVR treatment.

[b]RAV (for NS3) status at time of relapse or viral breakthrough with prior TVR treatment (tx) and RAV status at initiation of subsequent SMV treatment may or may not have been different as indicated within parenthesis. NR indicates RAV status not reported.

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Authors' Conclusions

"In conclusion, the treatment outcome of simeprevir based triple therapy for HCV genotype 1b patients with prior telaprevir failure depended on the prior response to PEG-IFNa and ribavirin. There is a good possibility of SVR for treatment-naiive patients and for those with prior relapse or partial response to PEG-IFNa and ribavirin, particularly because of the improvement of treatment adherence. In contrast, there is little hope of achieving SVR for patients with prior null response. In this era of diversified options for the treatment of chronic hepatitis C with the introduction of various DAAs, our study provides useful information for tailoring treatment options in the future." Page 999

Wilson,[21] 2016, USA

Main Findings

Outcomes with LDV/SOF in patients with HCV GT-1 infection who had failed prior therapy with DAAs

RAV status prior to retreatment	No. of patients	Outcome
With NS5B variant	0	-
With NS5A variant	28	25 achieved SVR12 2 withdrew 1 relapsed
With NS5A and NS5B variants	1	1 achieved SVR12
With no NS5A or NS5B variant	5	5 achieved SVR12

Considering all patients (N = 34), SVR was achieved by 91.2%

Authors' Conclusions

"In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants." Page 280

Zeumen,[22] 2016, USA, Europe (LEAUGE-1)

Relevant findings:

SVR12 with (DCV+SMV±R) in patients with HCV, GT-1b and with or without NS3 polymorphism

Patient category: with or without NS3 polymorphism at baseline	Proportion achieving SVR12, ratio (%)
With V36I polymorphism	3/3 (100.0)
Without V36I polymorphism	110/135 (80.7)
With T54S polymorphism	4/4 (100.0)
Without T54S polymorphism	109/134 (80.6)
With Q80L polymorphism	1/4 (25.0)
Without Q80L polymorphism	112/134 (82.8)
With S122G/N/T polymorphism	20/25 (80.0)
Without S122G/N/T polymorphism	93/113 (81.4)
With V36I, T54S, Q80L, or S122G/N/T polymorphism	24/30 (80.0)
Without V36I, T54S, Q80L, or S122G/N/T polymorphism	89/108 (81.5)

Table A6: Summary of Findings of Included Clinical Studies

Main Study Findings and Author's Conclusions

Authors' Conclusions

"In conclusion, the efficacy and safety of DCV + SMV, with or without RBV, was demonstrated in treatment-naive patients and null responders with genotype 1b infection. DCV + SMV was effective alone or in combination with RBV and with a 12- week treatment duration. SVR12 rates were higher in patients without NS5A polymorphisms at baseline." Page. 299

Zeumen,[25] 2015, USA, Europe, Australia, Scandanavia, Asia, (C-EDGE)

Relevant findings:

Outcomes with (EBR+GRZ) in patients with HCV GT1, GT 4 or GT6 infections

HCV genotype	RAV status at baseline	Proportion of patients achieving SVR12, ratio (%)
GT1a	With NS3 RAV	83/86 (97)
	Without NS3 RAV	58/65 (89)
GT1b	With NS3 RAV	24/25 (96)
	Without NS3 RAV	104/104 (100)
GT4	With NS3 RAV	7/7 (100)
	Without NS3 RAV	11/11 (100)
GT6	With NS3 RAV	7/9 (78)
	Without NS3 RAV	NA (All had NS3 RAV)

Prevalence of NS3 RAVs

At baseline, NS3 RAVs were identified in 86 of 151 (57 %) GT1a infected patients
At baseline, NS3 RAVs were identified in 25 of 129 (19 %) GT1b infected patients
At baseline, NS3 RAVs were identified in 7 of 18 (39%) GT4 infected patients
At baseline, NS3 RAVs were identified in 9 of 9 (100%) GT6 infected patients

Authors' Conclusions

"Grazoprevir-elbasvir achieved high SVR12 rates in treatment-naïve cirrhotic and noncirrhotic patients with genotype 1, 4, or 6 infection. This once dailyall-oral, fixed combination regimen represents a potent new therapeutic option for chronic HCV infection." Page 1

ASV = asunaprevir, BOC = boceprevir, CI = confidence interval, EBR = elbasvir, GT = genotype, GZR = grazoprevir, HCV = hepatitis c virus, NR = not reported, OR = odds ratio, PR = pegylated interferon and ribavirin, R (or RBV) = ribavirin, RAV = resistance associated variant, SE = Shannon entropy, SOF = sofobuvir, SMV = simeprevir, SVR = sustained virological response, TVR = telaprevir